From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION
(PCT Rule 66)

To:

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Date of mailing *(day/month/year)*	15.06.2004
Applicant's or agent's file reference: P1312 PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/29062	16.09.2003	22.10.2002

International Patent Classification (IPC) or both national classification and IPC
A61K48/00, A61K48/00

Applicant
MEDTRONIC AVE, INC.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22.02.2005

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MDC ___
RED BOOK ___
2nd Review ___
Resp to RWO
15 Sept 2004

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-19

   because:

   ☒ the said international application, or the said claims Nos. 1-19 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-28
Inventive step (IS)	Claims	1-28
Industrial applicability (IA)	Claims	20-28

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

D1: WO 97/16169 A (CHIRON CORP) 9 May 1997

D2: SHARIFI BEHROOZ G ET AL: "Adeno-associated virus-mediated apo A-I milano genetherapy for atherosclerosis and restenosis" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001, pages 270A-271A

D3: CHEN M ET AL: "DEVELOPMENT AND CHARACTERIZATION OF A RECOMBINANT TRUNCATED TYPE VII COLLAGEN MINIGENE" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, vol. 275, no. 32, 11 August 2000, pages 24429-24435

D4: SHAH PREDIMAN K ET AL: "High-dose recombinant apolipoprotein A-Imilano mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein E-deficient mice: Potential implications for acute plaque stabilization" CIRCULATION, vol. 103, no. 25, 26 June 2001, pages 3047-3050

D5: CHIESA GIULIA ET AL: "Recombinant apolipoprotein A-IMilano infusion into rabbit carotid artery rapidly removes lipid from fatty streaks" CIRCULATION RESEARCH, vol. 90, no. 9, 17 May 2002, pages 974-980

D6: BARNES MICHAEL J ET AL: "Collagens and atherosclerosis" EXPERIMENTAL GERONTOLOGY, vol. 34, no. 4, July 1999, pages 513-525

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty

The subject-matter of claims 1-11, 15-19 lacks novelty under Art. 33(1) and (2) PCT over the disclosure of D1 teaching the use of gene therapy in the treatment and prevention of cardiovascular diseases including plaque rupture. The subject-matter of claims 20,21,23-26,28 lacks novelty over D2 disclosing adeno-associated virus coding apo A-I Milano and the use thereof for the treatment of atherosclerosis. The subject-matter of claims 20-22, 25,26,28 lacks novelty under over the disclosure of D3 teaching eucaryotic expression vector coding truncated collagen VII gene.

The subject-matter of claims 12-14 is considered to be novel under Art. 33(1) and (2) PCT as none of the cited documents teaches the use of a nucleic acid coding for a collagen isoform or apolipoprotein A1 isoform in the treatment of vulnerable plaque.

Inventiveness

As the subject-matter of claims 1-11, 15-28 is considered as lacking novelty, no inventiveness can be acknowledged in this stage.

The subject-matter of claims 13,14 is considered as lacking an inventive step under Art. 33(1) and (3) PCT for the following reasons: The beneficial effect of Apo A1 Milano on vulnerable plaque stabilisation is known from D4 and D5. Taking into the account this known activity, it would be obvious to a person skilled in the art to employ nucleic acid coding for Apo A1 in the method of gene therapy for preventing plaque rupture as known from D1. Furthermore, the application does not prove that the claimed solution actually solves the technical problem as there are no experimental data showing any effect of the gene therapy as claimed on the vulnerable plaque.

The subject-matter of claim 12 is considered as lacking an inventive step under Art. 33(1) and (3) PCT for the following reasons: It is known from D6 that collagen type I plays the pivotal role in plaque stability and that an important factor leading to plaque

instability is proteolysis of collagen(s) in the cap by metalloproteinases. Taking into the consideration this disclosure of D5, it would be obvious to a person skilled in the art to use a collagen isoform gene in the method known form D1. Furthermore, analogically as in the case of Apo A1 Milano gene above, there is no prove in the application that the solution claimed in claim 12 actually solves the technical problem.

Industrial applicability

Subject-matter of independent claims 20-28 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 1-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.